Mesenchymal-Stem-Cell-Induced Immunoregulation Involves FAS-Ligand-/FAS-Mediated T Cell Apoptosis.

Journal: Cell Stem Cell

Publication Year: 2012

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PubMed link: 22542159

Funding Grants: Oral and Craniofacial Reconstruction Using Mesenchymal Stem Cells

Public Summary:
Mesenchymal stem cells (MSCs) are a population of adult stem cells with the potential to become bone forming cells, cartilage cells, and fat cells. MSCs are a promising cell source for bone and soft tissue regeneration to replace damaged and diseased tissues. Additionally, MSCs are capable of regulating immune cells by inhibiting proliferation and function of several major immune cells, such as dendritic cells, T and B lymphocytes, and natural killer (NK) cells. Systemic infusion of MSCs has been successfully used in treatment of various human diseases, including graft versus host disease (GvHD), systemic lupus erythematosus (SLE), rheumatoid arthritis, autoimmune encephalomyelitis, inflammatory bowel disease, and multiple sclerosis. However, the detailed mechanism in which BMMSCs regulate immune function is largely unknown. In this study, we find that systemic infusion of MSCs can induce a transient T cell death by a typical death pathway, name Fas Ligand (FasL)-mediated Fas pathway, and cure systemic sclerosis (SS) and colitis in mouse models. The therapeutic mechanism of MSC infusion is associated with phagocytosis of dead T cell debris, leading to a high level of macrophage-mediated transforming growth factor beta (TGF-↑) production and a subsequent reduced immune system response. Importantly, we find that MSC infusion in SS patients resulted in a T cell death and reduced immune response. Additionally, we reveal that MSCs without Fas receptor, with normal FasL function, cannot induce T cell death and fail to offer treatment effect for SS and colitis mice. Mechanistic study shows that Fas controls a chemokine, named monocyte chemotactic protein 1 (MCP-1), secretion in BMSCs, which plays a crucial role in the recruitment of T cells to MSCs for FasL-induced cell death. In summary, MSCs use Fas to control MCP-1 secretion for the recruitment of T cells and subsequently use FasL to induce T cell death. Macrophages take debris of dead T cells to release a high level of TGF-↑, leading to reduced immune response for immune therapies. This study uncovers the role of Fas and FasL in MSC-based immune therapies, which may serve as a basis to develop new strategies for improving cell-based therapies. The significance of this study is to identify a novel mechanism of MSC-associated immunomodulation and immune therapy.

Scientific Abstract:
Systemic infusion of bone marrow mesenchymal stem cells (BMMSCs) yields therapeutic benefit for a variety of autoimmune diseases, but the underlying mechanisms are poorly understood. Here we show that in mice systemic infusion of BMMSCs induced transient T cell apoptosis via the FAS ligand (FASL)-dependent FAS pathway and could ameliorate disease phenotypes in fibrillin-1 mutated systemic sclerosis (SS) and dextran-sulfate-sodium-induced experimental colitis. FASL(-/-) BMMSCs did not induce T cell apoptosis in recipients, and could not ameliorate SS and colitis. Mechanistic analysis revealed that FAS-regulated monocyte chemotactic protein 1 (MCP-1) secretion by BMMSCs recruited T cells for FASL-mediated apoptosis. The apoptotic T cells subsequently triggered macrophages to produce high levels of TGFbeta, which in turn led to the upregulation of CD4(+)CD25(+)Foxp3(+) regulatory T cells and, ultimately, immune tolerance. These data therefore demonstrate a previously unrecognized mechanism underlying BMMSC-based immunotherapy involving coupling via FAS/FASL to induce T cell apoptosis.